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13. ABSTRACT (Maximum 200 words)

The aims of this research project were to investigate the involvement of opiate and GABAergic systems, in different brain regions, in regulating the storage of memory for different types of tasks. The proposed experiments were based on previous findings providing extensive evidence that memory storage is influenced by treatments affecting neuromodulatory systems in the amygdala as well as preliminary evidence suggesting the possibility that such influences might be limited to restricted domains (or forms) of learning and memory. The view that GABAergic and opiate drugs act by influencing memory storage is supported by previous, as well as recent evidence that the drugs do not induce state-dependency. That is, the effects on retention performance do not depend upon a congruence between drug states a the time of training (or shortly after training) and retention testing. The research supported by this grant has provided additional evidence that memory storage is influenced by opiate and GABAergic influences. Within the range of tasks examined, the effects did not depend upon the forms of learning and memory examined. Both the amygdala and septum appear to be involved in regulating GABAergic influences on memory and the effects appear to be mediated through cholinergic influences.

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Project Title: Analysis of Neural Systems Involved in the Modulation of Memory Storage

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The aims of this research project were to investigate the involvement of opiate and GABAergic systems, in different brain regions, in regulating the storage of memory for different types of tasks. The proposed experiments were based on previous findings providing extensive evidence that memory storage is influenced by treatments affecting neuromodulatory systems in the amygdala as well as preliminary evidence suggesting the possibility that such influences might be limited to restricted domains (or forms) of learning and memory. The view that GABAergic and opiate drugs act by influencing memory storage is supported by previous, as well as recent (Castellano and McGaugh,1990) evidence that the drugs do not induce state-dependency. That is, the effects on retention performance do not depend upon a congruence between drug states a the time of training (or shortly after training) and retention testing.

In a series of experiments (Nagahara and McGaugh, 1992a;1992b) we examined the effects of the GABAergic agonist muscimol on learning and retention of a variety of tasks, including inhibitory avoidance, water maze place learning and rewarded alternation. Muscimol infused into the medial septum prior to training produced dose-dependent impairment of long-term retention in each task. In all tasks, retention was unimpaired shortly after the training. Retention was not influenced by posttraining injections. These findings suggest that GABAergic influences in the medial septum (which are known to regulate hippocampal muscarinic cholinergic functioning) regulate the long-term storage of information but that short term memory is independent of such influences. Furthermore they indicate that the effects are seen in a variety of training tasks sampling several "forms" of learning.

Other experiments examined the interaction of GABAergic and opiate systems with other neuromodulatory systems in regulating memory storage and the role of the amygdala in integrating such interactions. Findings from this laboratory as well, as many other laboratories, indicate that retention of inhibitory avoidance training is impaired and enhanced, respectively, by systemic injections of GABAergic agonists and antagonists. We recently found that the effects of GABAergic drugs on retention is blocked by lesions of the amygdala (Ammassari-Teule, Pavone, Castellano and McGaugh, 1991). These findings strongly suggest that the effects of GABAergic drugs on memory are mediated, at least in part, by the amygdala. The findings are also consistent with our findings that the effects of benzodiazepines on retention of inhibitory avoidance training are blocked by lesions of the amygdaloid complex. In a first experiment (Tomaz, Dickinson-Anson and McGaugh, 1991) we found that systemic injections of diazepam prior to training produced dose-dependent impairment of retention and that such effects were blocked in animals with NMDA-induced lesions of the amygdaloid complex. In a second experiment (Tomaz, Dickinson-Anson and McGaugh, 1992) we found that diazepam-induced amnesia was blocked by lesions of the basolateral nucleus of the amygdala but not by lesions of the central nucleus. These findings are of importance in relation to our studies of the effects of GABAergic agonists and antagonists because benzodiazepines are known to act through influences on GABAergic activity.

In studies using systemic injections (Castellano and McGaugh, in press) we have obtained additional findings suggesting that opiate and GABAergic drugs influence memory through a common mechanism. Low and otherwise effective doses of muscimol and β–administered together after training impair retention. Furthermore, the retention-impairing effects of a high dose of β–endorphin are blocked by concurrent administration of a low and otherwise ineffective dose of the GABAergic antagonist bicuculline. In an extensive series of previous experiments we obtained findings suggesting that the effects of opiate and GABAergic drugs on memory are mediated by influences on the release of norepinephrine (NE) within the amygdaloid complex. Recent findings (unpublished) of studies using intra-amygdala injections provide additional support for this view. The retention-enhancing effects of the GABAergic antagonist bicuculline were blocked by propranolol and the retention-impairing effects of β-endorphin were blocked by concurrent infusion of low doses of the adrenergic agonist clenbuterol. Furthermore, low and otherwise ineffective doses of the adrenergic antagonist propranolol and β-endorphin impaired retention when injected concurrently into the amygdala after training. Highly similar results were obtained in studies using two tasks, and inhibitory avoidance task and a water-maze spatial task.

Cholinergic effects also appear to be involved in GABAergic and noradrenergic influences on memory storage. The retrograde amnesia induced by systemic injections of GABAergic agonists is attenuated by low doses of the muscarinic cholinergic agonist oxotremorine (Castellano and McGaugh, 1991). In experiments (unpublished) using intra-amygdala injections we found that the retention-enhancing effects of clenbuterol were blocked by a low dose of the cholinergic antagonist atropine. In addition, a low dose of propranolol administered together with muscimol lowered the dose of muscimol required for inducing retention impairment. These findings are consistent with other evidence from this laboratory suggesting that GABAergic influences on memory involve NE and that the effects are mediated, in turn, through influences involving a muscarinic cholinergic mechanism.

In summary, the research supported by this grant has provided additional evidence that memory storage is influenced by opiate and GABAergic influences. Within the range of tasks examined, the effects did not depend upon the forms of learning and memory examined. Both the amygdala and septum appear to be involved in regulating GABAergic influences on memory and the effects appear to be mediated through cholinergic influences.

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